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MD Research News

Issue 66

Tuesday February 7, 2012

This free weekly bulletin lists the latest published research articles on macular degeneration (MD) as indexed in the NCBI, PubMed (Medline) and Entrez (GenBank) databases. These articles were identified by a search using the key term “macular degeneration”.

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Drug treatment

Expert Opin Pharmacother. 2012 Feb 3. [Epub ahead of print]

Intravitreal aflibercept injection for neovascular (wet) age-related macular degeneration.

Ohr M, Kaiser PK.

Cole Eye Institute, Cleveland Clinic , 9500 Euclid Ave, Desk i3, Cleveland, OH 44195 , USA +1 216 444 6702 ; +1 216 445 2226 ; pkkaiser@aol.com.

Introduction: Age-related macular degeneration (AMD) continues to be a leading cause of blindness worldwide. The neovascular form of the disease can lead to rapid and progressive vision loss. Vascular endothelial growth factor (VEGF) has emerged as a key target of treatment, with inhibitors of VEGF being shown to arrest the angiogenic process and avoid the visual damage typically associated with its presence.

Areas covered: This manuscript reviews the treatment history for wet AMD and examines aflibercept, a new, fully human, recombinant fusion protein designed to bind all isoforms of VEGF-A, as well as placental growth factor (PGF), thereby inhibiting the binding and activation of VEGF receptors.

Expert opinion: The results of Phase I, II and III studies have proven aflibercept to be a safe and effective treatment for wet AMD. Recent results of Phase III studies demonstrate the efficacy of aflibercept, dosed every 8 weeks after three initial monthly doses, and show that this regimen is clinically equivalent to monthly ranibizumab therapy. Eylea™ (aflibercept) was approved by the FDA for the treatment of wet AMD on 18 November 2011.

PMID: 22300011 [PubMed - as supplied by publisher]

Retina. 2012 Jan 31. [Epub ahead of print]

OPTIMIZING INDIVIDUALIZED THERAPY WITH BEVACIZUMAB FOR NEOVASCULAR AGE-RELATED MACULAR DEGENERATION.

Patel PJ, Tufail A; for the ABC Trial Investigators.

NIHR Biomedical Research Centre for Ophthalmology, Moorfields Eye Hospital and UCL Institute of Ophthalmology, London, United Kingdom.

PURPOSE: The purpose of this study was to evaluate a standardized retreatment strategy with intravitreal bevacizumab in the treatment of neovascular age-related macular degeneration.

METHODS: In this double-masked randomized trial, patients with neovascular age-related macular degeneration were randomized to intravitreous bevacizumab or standard care. Bevacizumab treatment was given at 6 weekly intervals with 3 consecutive injections (loading phase) followed by variable dosing to Week 54 using standardized retreatment criteria.

RESULTS: Three hundred and eighty retreatment decisions were made after 3 fixed injections for 64 patients randomized to bevacizumab that completed 1-year follow-up. The most common criterion for retreatment was persistent intraretinal fluid on optical coherence tomography imaging, and fluorescein angiography did not drive any retreatment decision. The mean (median) change in visual acuity and optical coherence tomography central macular thickness after the 3 loading treatments to Week 54 was +0.4 (+1.0) letters and +2.0 (+1.0) μm, respectively, with a mean (median) of 7.1 (7.0) injections. The median time to retreatment was 42 days with 12 of 69 injection-free episodes (17%) lasting more than 3 months.

CONCLUSION: Sustained improvements in structure and function were achieved using this 6 weekly variable-dosing regimen with intravitreal bevacizumab. Most retreatment decisions were based on qualitative interpretation of optical coherence tomography scans.

PMID: 22298014 [PubMed - as supplied by publisher]

Angiogenesis. 2012 Feb 3. [Epub ahead of print]

Binding and neutralization of vascular endothelial growth factor (VEGF) and related ligands by VEGF Trap, ranibizumab and bevacizumab.

Papadopoulos N, Martin J, Ruan Q, Rafique A, Rosconi MP, Shi E, Pyles EA, Yancopoulos GD, Stahl N, Wiegand SJ.

Regeneron Pharmaceuticals Inc., 777 Old Saw Mill River Road, Tarrytown, NY, 10591, USA.

Abstract

Pharmacological inhibition of VEGF-A has proven to be effective in inhibiting angiogenesis and vascular leak associated with cancers and various eye diseases. However, little information is currently available on the binding kinetics and relative biological activity of various VEGF inhibitors. Therefore, we have evaluated the binding kinetics of two anti-VEGF antibodies, ranibizumab and bevacizumab, and VEGF Trap (also known as aflibercept), a novel type of soluble decoy receptor, with substantially higher affinity than conventional soluble VEGF receptors. VEGF Trap bound to all isoforms of human VEGF-A tested with subpicomolar affinity. Ranibizumab and bevacizumab also bound human VEGF-A, but with markedly lower affinity. The association rate for VEGF Trap binding to VEGF-A was orders of magnitude faster than that measured for bevacizumab and ranibizumab. Similarly, in cell-based bioassays, VEGF Trap inhibited the activation of VEGFR1 and VEGFR2, as well as VEGF-A induced calcium mobilization and migration in human endothelial cells more potently than ranibizumab or bevacizumab. Only VEGF Trap bound human PlGF and VEGF-B, and inhibited VEGFR1 activation and HUVEC migration induced by PlGF. These data differentiate VEGF Trap from ranibizumab and bevacizumab in terms of its markedly higher affinity for VEGF-A, as well as its ability to bind VEGF-B and PlGF.

PMID: 22302382 [PubMed - as supplied by publisher]

Ophthalmology. 2012 Jan 31. [Epub ahead of print]

Ranibizumab for Macular Edema Due to Retinal Vein Occlusions Long-term Follow-up in the HORIZON Trial.

Heier JS, Campochiaro PA, Yau L, Li Z, Saroj N, Rubio RG, Lai P.

Ophthalmic Consultants of Boston, Boston, Massachusetts.

PURPOSE: To assess long-term safety and efficacy of intraocular ranibizumab injections in patients with macular edema after retinal vein occlusion (RVO).

DESIGN: Open-label extension trial of the 12-month Ranibizumab for the Treatment of Macular Edema following Branch Retinal Vein Occlusion: Evaluation of Efficacy and Safety (BRAVO) and Central Retinal Vein Occlusion Study: Evaluation of Efficacy and Safety (CRUISE) trials.

PARTICIPANTS: We included 304 patients who completed BRAVO and 304 patients who completed CRUISE.

METHODS: Patients were seen at least every 3 months and given an intraocular injection of 0.5 mg ranibizumab if they met prespecified retreatment criteria.

MAIN OUTCOME MEASURES: Primary outcomes were incidence and severity of ocular and nonocular adverse events (AEs). Key efficacy outcomes included mean change from baseline best-corrected visual acuity (BCVA) letter score by Early Treatment Diabetic Retinopathy Study protocol and central foveal thickness.

RESULTS: In patients who completed month 12, the mean number of injections (excluding month 12 injection) in the sham/0.5-, 0.3/0.5-, and 0.5-mg groups was 2.0, 2.4, and 2.1 (branch RVO) and 2.9, 3.8, and 3.5 (central RVO), respectively. The incidence of study eye ocular serious AEs (SAEs) and SAEs potentially related to systemic vascular endothelial growth factor inhibition across treatment arms was 2% to 9% and 1% to 6%, respectively. The mean change from baseline BCVA letter score at month 12 in branch RVO patients was 0.9 (sham/0.5 mg), -2.3 (0.3/0.5 mg), and -0.7 (0.5 mg), respectively. The mean change from baseline BCVA at month 12 in central RVO patients was -4.2 (sham/0.5 mg), -5.2 (0.3/0.5 mg), and -4.1 (0.5 mg), respectively.

CONCLUSIONS: No new safety events were identified with long-term use of ranibizumab; rates of SAEs potentially related to treatment were consistent with prior ranibizumab trials. Reduced follow-up and fewer ranibizumab injections in the second year of treatment were associated with a decline in vision in central RVO patients, but vision in branch RVO patients remained stable. Results suggest that during the second year of ranibizumab treatment of RVO patients, follow-up and injections should be individualized and, on average, central RVO patients may require more frequent follow-up than every 3 months.

PMID: 22301066 [PubMed - as supplied by publisher]

Clin Ther. 2012 Jan 28. [Epub ahead of print]

Cost-Effectiveness Analysis of Ranibizumab versus Verteporfin Photodynamic Therapy, Pegaptanib Sodium, and Best Supportive Care for the Treatment of Age-Related Macular Degeneration in Greece.

Athanasakis K, Fragoulakis V, Tsiantou V, Masaoutis P, Maniadakis N, Kyriopoulos J.

Department of Health Economics, National School of Public Health, Athens, Greece.

BACKGROUND: Age-related macular degeneration (AMD) is a progressive disease that results in loss of central vision, significant functional impairment, and a subsequent heavy socioeconomic burden. AMD treatments delay disease progression, improve patient outcomes, and reduce resource use associated with visual impairment, however, in a varying way concerning costs and effects.

OBJECTIVE: The purpose of this study was to investigate the cost effectiveness of ranibizumab compared with verteporfin photodynamic therapy, pegaptanib sodium, and best supportive care for the treatment of AMD in Greece.

METHODS: A 6-state Markov model was constructed according to patient visual acuity in the better-seeing eye. Data on effectiveness were derived from randomized controlled trials evaluating the outcomes of ranibizumab versus alternative AMD treatments. Resource utilization reflected the Greek health care setting

and was defined by a panel of experts. All treatments were administered for a 2-year period and evaluated during a 10-year time frame from a third-party payer perspective and discounted at 3.5% per annum.

RESULTS: Estimated mean 10-year direct costs of treatment in the ranibizumab arm ranged from €23,733 to €31,795 (2011 Euros), with a projected gain of 4.50 to 4.74 quality-adjusted life years (QALYs) or 2.97 to 4.47 vision years, depending on type of lesion. For predominantly classic lesions, the cost per QALY gained with ranibizumab was estimated at €6444/QALY (95% uncertainty interval [UI], €-30,403/QALY to €44,524/QALY), €15,344 (95% UI, €-11,433 to €53,554) and dominant relative to photodynamic therapy, best supportive care, and pegaptanib, respectively. Corresponding ratios for patients with minimally classic lesions were €24,580/QALY (95% UI, €-5580/QALY to €76229/QALY) and €13,112/QALY (95% UI, €-3839/QALY to €37,527/QALY) for ranibizumab relative to best supportive care and pegaptanib, and for patients with occult lesions were estimated at €19,407/QALY (95% UI, €-1486 to €46,434) and €28,561/QALY (95% UI, €6143 to 73,431), respectively. Sensitivity analysis provided robust results in all cases.

CONCLUSION: Ranibizumab can be a cost-effective option for the treatment of AMD compared with selected alternatives in the Greek health care setting.

PMID: 22289279 [PubMed - as supplied by publisher]

J Cataract Refract Surg. 2012 Jan 25. [Epub ahead of print]

Outcomes of cataract surgery in patients with neovascular age-related macular degeneration in the era of anti-vascular endothelial growth factor therapy.

Tabandeh H, Chaudhry NA, Boyer DS, Kon-Jara VA, Flynn HW Jr.

From Retina Vitreous Associates Medical Group (Tabandeh, Boyer), Beverly Hills, California, New England Retina Associates (Chaudhry, Kon-Jara), New London, Connecticut, and Bascom Palmer Eye Institute (Flynn), Miami, Florida, USA.

PURPOSE: To evaluate the visual outcomes, choroidal neovascular complex status, and adverse events in patients with visually significant cataract and neovascular age-related macular degeneration (AMD) who had cataract surgery.

SETTING: Private practices, Beverly Hills, California, and New London, Connecticut, USA.

DESIGN: Case series.

METHODS: Data were abstracted from the medical records of patients with neovascular AMD treated by anti-vascular endothelial growth factor (anti-VEGF) therapy who had cataract surgery. The main outcome measures were Snellen corrected distance visual acuity (CDVA), perioperative adverse events, and status of the choroidal neovascular complex.

RESULTS: The study enrolled 30 eyes of 28 patients. The CDVA was 20/40 or better in 10% of eyes preoperatively and 40% postoperatively; 20/50 to 20/100 in 53% and 33%, respectively; and 20/200 or worse in 37% and 27%, respectively. The change in CDVA from preoperatively to postoperatively was statistically significant, with a mean change of 0.22 logMAR ± 0.27 (SD) at 2 months (P<.0001), 0.22 ± 0.36 logMAR at 6 months (P=.001), and 0.17 ± 0.54 logMAR at the last follow-up (P=.01). Patients received a mean of 0.32 injections per month postoperatively compared with 0.49 injections per month preoperatively. Perioperative macular adverse events did not occur in any eye.

CONCLUSIONS: With regular evaluations and appropriate treatment with anti-VEGF agents, cataract surgery did not appear to be associated with an increased incidence of perioperative complications or macular adverse events.

PMID: 22284725 [PubMed - as supplied by publisher]

Curr Med Res Opin. 2012 Jan 30. [Epub ahead of print]

Anti-vascular endothelial growth factor sequential therapy for neovascular age-related macular degeneration: is this the new deal?

Neri P, Mariotti C, Arapi I, Bambini E, Giovannini A.

Abstract

Abstract Objective: To review clinical data on the sequential use of the non-selective vascular endothelial growth factor (VEGF) inhibitors (ranibizumab and bevacizumab) and the selective VEGF inhibitor (pegaptanib) in the treatment of neovascular age related macular degeneration (n-AMD). Methods: This is a selective review of the literature based on a Pub Med search using the terms 'age-related macular degeneration', 'selective anti-VEGF', 'non-selective anti-VEGF', 'combination therapy' from 2000 to date in the English language. Studies on the management of n-AMD reporting adherence, patient-reported outcomes, costs, side effects, resource use and cost effectiveness were also included. Results: The trial data suggest that pan-VEGF inhibition provides improved treatment outcomes in patients with n-AMD with selective anti-VEGF agents offering better tolerability on long-term treatment. A pilot trial and a large-scale, multicentred study confirmed the long-term efficacy of a selective VEGF inhibitor when used as maintenance therapy. Importantly, there is evidence that selective VEGF inhibition also reduces the risks associated with pan-VEGF blockade in patients with n-AMD. Discussion: Anti-VEGF agents play a principal in the management of n-AMD. The most potent are the pan-VEGF agents although there is some discussion regarding their long-term tolerability. The sequential use of non-selective VEGF inhibitors as booster therapy with a selective VEGF inhibitor as maintenance therapy seems to offer a promising safety/efficacy profile, as well as improved cost/effectiveness.

PMID: 22283373 [PubMed - as supplied by publisher]

Other treatment & diagnosis

Eye (Lond). 2012 Feb;26(S1):S2-S21. doi: 10.1038/eye.2011.343.

Action on AMD. Optimising patient management: act now to ensure current and continual delivery of best possible patient care.

Amoaku W, Blakeney S, Freeman M, Gale R, Johnston R, Kelly SP, McLaughlan B, Sahu D, Varma D.

University Hospital, QMC, Nottingham, UK.

Abstract

In recent years, there have been significant advances in the clinical management of patients with wet age-related macular degeneration (wet AMD)-a rapidly progressing and potentially blinding degenerative eye disease. Wet AMD is responsible for more than half of registered severe sight impairment (blindness) in the United Kingdom, and patients who are being treated for wet AMD require frequent and long-term follow-up for treatment to be most effective. The clinical workload associated with the frequent follow-up required is substantial. Furthermore, as more new patients are diagnosed and the population continues to age, the patient population will continue to increase. It is thus vital that clinical services continue to adapt so that they can provide a fast and efficient service for patients with wet AMD. This Action on AMDdocument has been developed by eye health-care professionals and patient representatives, the Action on AMDgroup. It is intended to highlight the urgent and continuing need for change within wet AMD services. This document also serves as a guide for eye health-care professionals, NHS commissioners, and providers to present possible solutions for improving NHS retinal and macular services. Examples of good practice and service development are considered and can be drawn upon to help services meet the recommended quality of care and achieve best possible outcomes.

PMID: 22302094 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2012 Feb 1. [Epub ahead of print]

Automated Assessment of Drusen Using Three-dimensional Spectral-domain Optical Coherence Tomography.

Iwama D, Hangai M, Ooto S, Sakamoto A, Nakanishi H, Fujimura T, Domalpally A, Danis RP, Yoshimura N.

Department of Ophthalmology and Visual Sciences, Kyoto University Graduate School of Medicine, Kyoto, Japan.

Purpose: To compare automated assessment of macular drusen delineated by our originally-developed algorithm on 3-dimensional (3D) spectral-domain optical coherence tomography (SD-OCT) with the assessment by certificated graders on color fundus photographs in non-neovascular age-related macular degeneration (AMD).

Design: Prospective case series.

Methods: Automated assessment of macular drusen was performed using raster scan by 3D OCT-1000 (Topcon) in 18 eyes with non-neovascular AMD with at least one large druse (≥125μm) and predominantly soft indistinct drusen. We defined drusen as the regions that have the distance between the RPE and calculated Bruch's membrane lines > predefined threshold distances. We assessed the agreement on maximum drusen size and drusen area within grid between 3D SD-OCT and color fundus photographs, and false-negative, and false-positive drusen at each threshold distance.

Results: There was agreement or agreement within one step in all eyes in maximum drusen size, and 15 (83.3%) of the eyes in drusen area, except 6 pixels, regardless of threshold distances. However, the number of eyes with exact agreement in drusen area increased when the threshold distances were smaller than 4 pixels. In the 3 cases with disagreement in drusen area, false-negative drusen on 3D SD-OCT were characterized by being small in area and height.

Conclusion: Automated assessment of drusen parameters based on our algorithm on 3D SD-OCT, which was limited by the poor detection ability of small drusen, showed good agreement with the assessment by certified graders on color fundus photography in our subjects.

PMID: 22297491 [PubMed - as supplied by publisher]

Graefes Arch Clin Exp Ophthalmol. 2012 Jan 31. [Epub ahead of print]

Relationship between retinal morphological findings and visual function in age-related macular degeneration.

Akagi-Kurashige Y, Tsujikawa A, Oishi A, Ooto S, Yamashiro K, Tamura H, Nakata I, Ueda-Arakawa N, Yoshimura N.

Department of Ophthalmology and Visual Sciences, Kyoto University Graduate School of Medicine, Sakyo-ku, Kyoto, 606-8507, Japan.

BACKGROUND: We aimed to study the retinal morphological findings associated with exudative age-related macular degeneration (AMD) and their association with visual prognosis.

METHODS: We retrospectively reviewed the medical records of 96 consecutive patients (96 eyes) with exudative AMD. Retinal structural changes were examined using optical coherence tomography (OCT).

RESULTS: Initial OCT examination showed cystoid macular edema in 18 eyes (18.8%), fibrin exudate in 56 eyes (58.3%), and hyperreflective foci within the neurosensory retina in 78 eyes (81.3%). Upon initial examination, an external limiting membrane (ELM) line was detected under the fovea in 64 eyes (66.7%). Using Pearson's correlation analyses, final visual acuity (VA) was correlated with initial VA ($r = 0.61$, $p < 0.001$), age ($r = 0.34$, $p < 0.001$), initial total foveal thickness ($r = 0.41$, $p < 0.001$), presence of

hyperreflective foci (r = 0.40, p < 0.001), and detection of a foveal ELM line (r = 0.55, p < 0.001). After multiple regression analysis, final VA correlated with initial VA (r = 0.48, p < 0.001), initial presence of hyperreflective foci (r = 0.23, p = 0.054), and detection of a foveal ELM line (r = 0.36, p = 0.008).

CONCLUSIONS: In eyes with exudative AMD, final VA was most correlated with initial VA. In addition, the initial integrity of the foveal outer retina was partially correlated with the visual prognosis. The initial ELM condition was associated with good final VA, while the initial presence of hyperreflective foci in the foveal neurosensory retina was associated with poor final VA.

PMID: 22290070 [PubMed - as supplied by publisher]

Ophthalmology. 2012 Jan 31. [Epub ahead of print]

Detection of New-Onset Choroidal Neovascularization Using Optical Coherence Tomography The AMD DOC Study.

Do DV, Gower EW, Cassard SD, Boyer D, Bressler NM, Bressler SB, Heier JS, Jefferys JL, Singerman LJ, Solomon SD.

Wilmer Eye Institute, The Johns Hopkins University School of Medicine, Baltimore, Maryland.

PURPOSE: To determine the sensitivity of time domain optical coherence tomography (OCT) in detecting conversion to neovascular age-related macular degeneration (AMD) in eyes at high risk for choroidal neovascularization (CNV), compared with detection using fluorescein angiography (FA) as the gold standard.

DESIGN: Prospective, multicenter, observational study.

PARTICIPANTS: Individuals aged ≥50 years with nonneovascular AMD at high risk of progressing to CNV in the study eye and evidence of neovascular AMD in the fellow eye.

METHODS: At study entry and every 3 months through 2 years, participants underwent best-corrected visual acuity, supervised Amsler grid testing, preferential hyperacuity perimetry (PHP) testing, stereoscopic digital fundus photographs with FA, and OCT imaging. A central Reading Center graded all images.

MAIN OUTCOMES MEASURES: The sensitivity of OCT in detecting conversion to neovascular AMD by 2 years, using FA as the reference standard. Secondary outcomes included comparison of sensitivity, specificity, positive predictive value, and negative predictive value of OCT, PHP, and supervised Amsler grid relative to FA for detecting incident CNV.

RESULTS: A total of 98 participants were enrolled; 87 (89%) of these individuals either completed the 24-month visit or exited the study after developing CNV. Fifteen (17%) study eyes had incident CNV confirmed on FA by the Reading Center. The sensitivity of each modality for detecting CNV was: OCT 0.40 (95% confidence interval [CI], 0.16-0.68), supervised Amsler grid 0.42 (95% CI, 0.15-0.72), and PHP 0.50 (95% CI, 0.23-0.77). Treatment for incident CNV was recommended by the study investigator in 13 study eyes. Sensitivity of the testing modalities for detection of CNV in these 13 eyes was 0.69 (95% CI, 0.39-0.91) for OCT, 0.50 (95% CI, 0.19-0.81) for supervised Amsler grid, and 0.70 (95% CI, 0.35-0.93) for PHP. Specificity of the OCT was higher than that of the Amsler grid and PHP.

CONCLUSIONS: Time-domain OCT, supervised Amsler grid, and PHP have low to moderate sensitivity for detection of new-onset CNV compared with FA. Optical coherence tomography has greater specificity than Amsler grid or PHP. Among fellow eyes of individuals with unilateral CNV, FA remains the best method to detect new-onset CNV.

PMID: 22297028 [PubMed - as supplied by publisher]

Insight. 2011 Fall;36(4):13-5.

The impact of vision loss from age-related macular degeneration: a review (Part 1).

Orticio LP.

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PMID: 22288233 [PubMed - in process]

Insight. 2011 Fall;36(4):10-2.

Age-related macular degeneration.

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PMID: 22288232 [PubMed - in process]

Pathogenesis

Med Hypotheses. 2012 Jan 30. [Epub ahead of print]

RPE cell senescence: A key contributor to age-related macular degeneration.

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Abstract

Age-related macular degeneration (AMD) is the leading cause of blindness in industrialized countries. Although much progress has been made recently in the management of later stages of the disease, no agents have yet been developed for the early stages or for prophylactic use. Furthermore, even the treatments for the later stages have limited effectiveness. The process of developing improved treatments for AMD is complicated by the existence of several theories concerning the cause of the disorder, each suggesting a different strategy for finding effective therapeutics. One of the potential contributors to AMD pathology is retinal pigment epithelial (RPE) cell senescence. The present paper hypothesizes that RPE senescence plays a central role in the etiology of AMD. This hypothesis is supported by the ability of RPE cell senescence to account for the signs, risk factors, and successful treatment modalities of the disorder. This hypothesis also points to several new prophylactic and treatment strategies for AMD.

PMID: 22296808 [PubMed - as supplied by publisher]

Curr Drug Targets. 2012 Jan 17. [Epub ahead of print]

∝7 nicotinic acetylcholine receptor subunit in Angiogenesis and Epithelial To Mesenchymal Transition.

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Abstract

Cigarette smoking is strongly correlated with many diseases like cancer, cardiovascular disease and macular degeneration. Nicotine, the main active and addictive component of tobacco smoke has recently been shown to enhance angiogenesis in many experimental systems and animal models. The pro-angiogenic activity of nicotine is mediated by nicotinic acetylcholine receptors, particularly the alpha 7 subunit, that are expressed on a variety of non-neuronal cells including those in the vasculature such as endothelial cells and smooth muscle cells. The present review focuses on the role of α7nAChR in mediating the pro-angiogenic effects of nicotine and describes the molecular mechanisms involved in nicotine-induced angiogenesis as well as epithelial to mesenchymal transition. These observations on nicotine function highlight the therapeutic potential of α7nAChR agonists and antagonists for combating angiogenesis related diseases.

PMID: 22300034 [PubMed - as supplied by publisher]

Mol Ther. 2012 Jan 31. doi: 10.1038/mt.2011.308. [Epub ahead of print]

Stanniocalcin-1 Rescued Photoreceptor Degeneration in Two Rat Models of Inherited Retinal Degeneration.

Roddy GW, Rosa Jr RH, Youn Oh J, Ylostalo JH, Bartosh TJ Jr, Choi H, Lee RH, Yasumura D, Ahern K, Nielsen G, Matthes MT, Lavail MM, Prockop DJ.

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Abstract

Oxidative stress and photoreceptor apoptosis are prominent features of many forms of retinal degeneration (RD) for which there are currently no effective therapies. We previously observed that mesenchymal stem/stromal cells reduce apoptosis by being activated to secrete stanniocalcin-1 (STC-1), a multifunctional protein that reduces oxidative stress by upregulating mitochondrial uncoupling protein-2 (UCP-2). Therefore, we tested the hypothesis that intravitreal injection of STC-1 can rescue photoreceptors. We first tested STC-1 in the rhodopsin transgenic rat characterized by rapid photoreceptor loss. Intravitreal STC-1 decreased the loss of photoreceptor nuclei and transcripts and resulted in measurable retinal function when none is otherwise present in this rapid degeneration. We then tested STC-1 in the Royal College of Surgeons (RCS) rat characterized by a slower photoreceptor degeneration. Intravitreal STC-1 reduced the number of pyknotic nuclei in photoreceptors, delayed the loss of photoreceptor transcripts, and improved function of rod photoreceptors. Additionally, STC-1 upregulated UCP-2 and decreased levels of two protein adducts generated by reactive oxygen species (ROS). Microarrays from the two models demonstrated that STC-1 upregulated expression of a similar profile of genes for retinal development and function. The results suggested that intravitreal STC-1 is a promising therapy for various forms of RD including retinitis pigmentosa and atrophic age-related macular degeneration (AMD).

PMID: 22294148 [PubMed - as supplied by publisher]

Clin Ophthalmol. 2012;6:145. Epub 2012 Jan 19.

Tissue plasminogen activator (tPA) in the management of predominantly hemorrhagic age-related macular degeneration, milligram/milliliter or microgram/milliliter?

Boone NW, van Leeuwen RW.

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Netherlands.

PMID: 22291455 [PubMed - in process] PMCID: PMC3267534

Genetics

Neurobiol Aging. 2012 Jan 31. [Epub ahead of print]

Alzheimer's disease and age-related macular degeneration have different genetic models for complement gene variation.

Proitsi P, Lupton MK, Dudbridge F, Tsolaki M, Hamilton G, Daniilidou M, Pritchard M, Lord K, Martin BM, Craig D, Todd S, McGuinness B, Hollingworth P, Harold D, Kloszewska I, Soininen H, Mecocci P, Velas B, Gill M, Lawlor B, Rubinsztein DC, Brayne C, Passmore PA, Williams J, Lovestone S, Powell JF.

King's College London, Institute of Psychiatry, De Crespigny Park, London, UK.

Abstract

Alzheimer's disease (AD) and age-related macular degeneration (AMD) are both neurodegenerative disorders which share common pathological and biochemical features of the complement pathway. The aim of this study was to investigate whether there is an association between well replicated AMD genetic risk factors and AD. A large cohort of AD (n = 3898) patients and controls were genotyped for single nucleotide polymorphisms (SNPs) in the complement factor H (CFH), the Age-related maculopathy susceptibility protein 2 (ARMS2) the complement component 2 (C2), the complement factor B (CFB), and the complement component 3 (C3) genes. While significant but modest associations were identified between the complement factor H, the age-related maculopathy susceptibility protein 2, and the complement component 3 single nucleotide polymorphisms and AD, these were different in direction or genetic model to that observed in AMD. In addition the multilocus genetic model that predicts around a half of the sibling risk for AMD does not predict risk for AD. Our study provides further support to the hypothesis that while activation of the alternative complement pathway is central to AMD pathogenesis, it is less involved in AD.

PMID: 22300950 [PubMed - as supplied by publisher]

Aging (Albany NY). 2012 Jan 31. [Epub ahead of print]

Quantitative trait loci on chromosome 1 for cataract and AMD-like retinopathy in senescence-accelerated OXYS rats.

Korbolina EE, Kozhevnikova OS, Stefanova NA, Kolosova NG.

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Abstract

Age-related macular degeneration (AMD) and cataract are common age-related diseases in humans. Previously we showed that senescence-accelerated OXYS rats develop retinopathy and cataract, which are comparable to human AMD and senile cataract. Here we focused on the identification of quantitative trait loci (QTLs), which affect early-onset cataract and retinopathy in OXYS rats, using F2 hybrids bred by a reciprocal cross (OXYS×WAG and WAG×OXYS). Chromosome 1 showed significant associations between retinopathy and loci in the regions of markers D1Rat30 and D1Rat219 (QTL1) as well as D1Rat219 and D1Rat81 (QTL2); and between early cataract development with the locus in the region of the markers D1Rat219 and D1Rat81 (QTL2). To determine the effects of these QTLs, we generated two congenic strains by transferring chromosome 1 regions from OXYS into WAG background. Both congenic strains (named WAG/OXYS-1.1 and WAG/OXYS-1.2, respectively) display early cataract and retinopathy development. Thus, we confirmed that genes located in the analyzed regions of chromosome 1 are

associated with the development of these diseases in OXYS rats.

PMID: 22300709 [PubMed - as supplied by publisher]

Med Sci Monit. 2012 Feb 1;18(2):PR1-3.

A69S and R38X ARMS2 and Y402H CFH gene polymorphisms as risk factors for neovascular age-related macular degeneration in Poland - a brief report.

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Background: The wet form of age-related macular degeneration (ARMD) is a leading cause of irreversible blindness in Caucasians. Our purpose was to assess influence of gene polymorphisms A69S (rs10490924) and R38X (rs2736911) ARMS2 and Y402 (rs1061170) CFH on wet ARMD risk in a Polish population.

Material/Methods: 130 unrelated patients (90 with wet ARMD and 40 controls) took part in the study. Dry blood was used for DNA isolation. PCR amplification and gene sequencing were performed. In subjects with R38X and A69S, SNP gene cloning was used to exclude the possible combined variant.

Results: Homozygous Y402H and A69S conferred a significance risk of wet ARMD in Poland: Y402H odds ratio (OR) was 5.57 (95% confidence interval: 1.58-19.6), p=0.002; and A69S OR was 7.72 (95% confidence interval: 1.73-34.36), p=0.001. R38X is probably more common in healthy subjects: OR was 0.45 (95% confidence interval: 0.19-1.05), p=0.053.

Conclusions: The etiologic role in ARMD of A69S ARMS2 and Y402H CFH gene variants were confirmed in a Polish population for the first time. R38X variant of ARMS2 seems to be protective from wet ARMD.

PMID: 22293892 [PubMed - in process]

Epidemiology

Clin Experiment Ophthalmol. 2012 Feb 2. doi: 10.1111/j.1442-9071.2012.02765.x. [Epub ahead of print]

Asian age-related macular degeneration phenotyping study: rationale, design and protocol of a prospective cohort study.

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Background: Current knowledge of the phenotypic characteristics (e.g., clinical features, risk factors, natural history and treatment response) of age-related macular degeneration in Asians remains limited. This report summarizes the rationale and study design of a prospective observational study of Asian neovascular age-related macular degeneration, including polypoidal choroidovasculopathy variant.

Design: The Asian Age-related macular degeneration Phenotyping study is a prospective, observational clinical study of Asian patients with neovascular age-related macular degeneration or polypoidal choroidovasculopathy in three tertiary eye centres in Singapore.

Participants: The study aims to recruit 500 consecutive patients from the retinal clinics of three tertiary eye

centres in Singapore.

Methods: Standardized examination procedures include interviews, a comprehensive eye examination, digital photography of the retina, fundus fluorescein and indocyanine green angiography and spectral domain optical coherence tomography using a standardized protocol. Blood samples are collected for biochemical analyses, and stored for genetic and proteomic studies.

Main Outcome Measures: The aim of the study is to build a comprehensive database of clinical, angiographic, functional and natural history data of Asian AMD over a 12-month follow-up period.

Results: This article discusses the methodology and design of this prospective multi-centred study.

Conclusions: This study will provide in-depth longitudinal data of the evolution of clinical features, risk factors, natural history and treatment pattern and response of Asian age-related macular degeneration and polypoidal choroidovasculopathy, allowing unique insights into pathogenesis and the design of new treatment strategies.

PMID: 22299650 [PubMed - as supplied by publisher]

Clin Experiment Ophthalmol. 2012 Feb 2. doi: 10.1111/j.1442-9071.2012.02759.x. [Epub ahead of print]

Long-term outcomes of phacoemulsification cataract surgery performed by trainees and consultants in an Australian cohort.

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Background: It is unclear whether differences exist in surgical complication rates and long-term visual acuity (VA) outcomes between patients whose phacoemulsification cataract surgery was performed by ophthalmological trainees and those performed by consultants.

Design: Prospective clinical cohort study.

Participants: 1851 participants of the Cataract Surgery and Age-related Macular Degeneration study, aged ≥ 64 years, had cataract surgery performed at Westmead Hospital, Sydney. Methods: Surgical complication rates and VA at 24-month postoperative visits were compared between patients who were operated on by trainees and those operated on by consultants.

Main Outcome Measures: Surgical outcomes included operative complications recorded in surgical audit forms and 24-month postoperative VA.

Results: Of 1851 patients, 1274 (68.8%) were reviewed 24 months post-surgery. Of these, 976 had data on the type of surgeon who performed the operation. After excluding 152 challenging cases and three cases operated on by first-year trainees at the beginning of their training, 821 patients were included in this study, of those 498 operated on by trainees and 323 by consultants. Habitual VA ≥ 6/12 was achieved in 77.3% (385/498) and 74.3% (n = 240/323), respectively, of the two groups of patients 24-months postoperatively. Of 514 patients who had surgical audit data, the major complication rate was numerically greater, but not significantly different for the 330 trainee-operated (6.1%), compared with the 184 consultant -operated patients (2.7%, p = 0.091).

Conclusions: We found relatively comparable complication rates and visual outcomes after 2 years

between patients operated on by ophthalmological trainees and those by consultants, in a cataract surgical cohort at Westmead Hospital. © 2012 The Authors. Journal compilation © 2012 Royal Australian and New Zealand College of Ophthalmologists.

PMID: 22300362 [PubMed - as supplied by publisher]

Diet

Arch Biochem Biophys. 2012 Jan 20. [Epub ahead of print]

Surface plasmon resonance (SPR) studies on the interactions of carotenoids and their binding proteins.

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Abstract

The xanthophyll carotenoids lutein and zeaxanthin constitute the major carotenoids of the macular pigment in the human retina where they are thought to act in part to prevent light induced oxidative damage associated with age-related macular degeneration (AMD). The highly selective uptake of these pigments is mediated by specific carotenoid-binding proteins (GSTP1 and StARD3) recently identified in our laboratory. Carotenoids are hydrophobic in nature, so we first systematically optimized carotenoid preparations that are nano-dispersed in aqueous buffers, and then we used a new-generation surface plasmon resonance (SPR) protocol called FastStep™, which is significantly faster than conventional SPR assays. We have explored carotenoid-binding interactions of five proteins: human serum albumin (HSA), β-lactoglobulin (LG), steroidogenic acute regulatory domain proteins (StARD1, StARD3) and glutathione S- transferase Pi isoform (GSTP1). HSA and LG showed relatively weak interaction with carotenoids (K(D)>1μM). GSTP1 evidenced high affinity and specificity towards zeaxanthin and meso-zeaxanthin with K(D) values 0.14±0.02μM and 0.17±0.02μM, respectively. StARD3 expressed a relative high specificity towards lutein with a K(D) value of 0.59±0.03μM, whereas StARD1 exhibited a relatively low selectivity and affinity (K(D) >1μM) towards the various carotenoids tested.

PMID: 22286029 [PubMed - as supplied by publisher]